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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,389	10/07/2003	John H. Kenten	IGN-2005US02	7446

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/681,389	KENTEN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80 and 94-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80 and 94-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1-79 and 81-93 have been cancelled. Claims 80 and 94 have been amended. Claim 101 is new. No new matter was introduced by the amendments to claims 80 and 94 or by the new claim 101.

Claims 80 and 94-101 are pending and under examination.

Response to Amendment

2. The rejection of claims 80 and 94-100 under 35 U.S.C. § 112, second paragraph for being indefinite because they were dependent on cancelled claims 1, 20, 41, and 58 is withdrawn in response to Applicant's amendment to the claims on 06/19/2006 that remove reference to the cancelled claims.

New Rejections

Claim Rejections - 35 USC § 112, 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

4. Claims 80 and 94 recite the limitation of "the antibody to be detected". There is insufficient antecedent basis for this limitation in the claims.

** It is noted that claim 101 is dependent on claim 80 and claims 95-100 are dependent on claim 94.

5. Claims 80 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 80 and 94 are indefinite because the recitation of "a single epitope-containing segment " can be interpreted as either a segment comprising one epitope, in which case the terms "a single epitope-containing segment, the epitope containing segment comprising two or more identical epitopes" do not make sense, or as one segment comprising two or more epitopes.

Similarly, it is not clear what the Applicant means by "a ubiquitin fusion protein comprising a heat shock protein fused to two or more non-contiguous epitope-containing segments".

Therefore, the metes and bounds of the claims cannot be determined and the claims are indefinite.

** It is noted that claim 101 is dependent on claim 80 and claims 95-100 are dependent on claim 94.

6. Claims 80 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 80 and 94 recites the broad recitation heat shock protein, and the claim also recites ubiquitin, which is the narrower statement of the range/limitation.

** It is noted that claim 101 is dependent on claim 80 and claims 95-100 are dependent on claim 94.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 94-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of neutralizing the biological function of a predetermined protein by immunizing an animal with a DNA encoding for the claimed fusion protein, does not reasonably provide enablement for a method of reducing the levels of a predetermined protein by immunizing an animal with a DNA encoding for the claimed fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

Claims 94-100 are drawn to a method for reducing the levels of a predetermined protein in an animal relative to base-line levels by eliciting an immune response against epitopes from the predetermined protein, wherein the protein can be a peptide

hormone, growth hormone, or tumor necrosis factor. Therefore, the Applicant contemplates to use antibodies directed against the predetermined protein to reduce its level of expression. At the time the invention was made, and even in the present, the art of using antibody to neutralize and reduce the levels of target proteins (i.e., to clear the immune complexes) was known to be unpredictable. For example, Rehlaender et al. (Pharmaceutical Research, 1998, 15: 1652-1653) teach:

> "If the antigen provides only a few binding sites for antibody or if either antibody or antigen is in a large molar excess, then smaller and less extensively crosslinked soluble immune complexes are formed.
>
> [b]oth complement-dependent and complement-independent clearance mechanisms for soluble immune complexes require crosslinking of immunoglobulin molecules by multivalent antigens.
>
> An antigen with only one combining site for antibody is incapable of crosslinking antibodies and hence would not be subject to the normal immune clearance mechanism.
>
> Some researchers attempting to use antibodies to neutralize undesirable cytokines were surprised to find that the biological activity of the cytokines often increased with the antibody therapy. Although anti-cytokine antibodies with sufficiently high avidity (Ka > 10^{10}-10^{12}) have been reported to be capable of neutralizing cytokine activity, numerous reports indicate that similar antibodies, presumably of lower avidity, can actually enhance the overall effect of their corresponding cytokines. Antibodies against IL-2, IL-3, IL-4, IL-6, and IL-7 have been found to prolong the circulation and pharmacological effect of these cytokines, apparently because the antibodies act as carrier proteins.

Hence, from the nature of the invention, one of skill in the art would not reasonably predict that an immune response elicited by a DNA encoding for an ubiquitin fused to a predetermined protein would always result in reducing the levels of that predetermined protein.

While the art teaches the use of vaccines to elicit neutralizing antibodies against the desired antigens, wherein the neutralizing antibodies interfere with the function of the antigen, the art does not teach that a vaccine can be used to reduce the expression

level of antigens. For example, Talwar (Human Reproduction, 1997, 3: 301-310) teaches:

> "The progress and current status of vaccines which induce antibodies against human chorionic gonadotrophin (HCG) and luteinizing hormone-releasing hormone (LHRH) are reviewd.
>
> Immunization with the vaccines prevents pregnancy, as long as the antibody titers remain ≥ 50 ng/ml HCG bioneutralizing capacity.
>
> The rationale of birth control vaccines is to induce the formation of antibodies and or elicitation of cell mediated immunity (CMI), competent to intercept the action of a hormone or a gamete antigen crucial to the success of reproduction."

Given the unpredictable outcome of using vaccination to reduce the levels of predetermined proteins, the specification should provide sufficient guidance and /or working examples that specifically address the use of vaccines as being effective in reducing the levels of the predetermined proteins to enable one of ordinary skills in the art to use such without undue experimentation. However, the specification only discloses examples demonstrating that vaccination against gonadotropin releasing hormone (GnGH), results in the induction of high levels of anti-GnGH antibodies and reduced levels of testosterone in serum i.e., the examples demonstrates neutralization of GnGH bioactivity. The specification does not provide examples demonstrating that the levels of GnGH (i.e., the predetermined protein) are indeed reduced following vaccination. Additionally, the specification provides an example of vaccination against growth hormone in pigs that results in enhanced growth rate, i.e., the activity of growth hormone is increased because the antibodies prolong its circulation and do not reduce its level. Therefore, the specification does not provide the guidance or the working examples required to overcome the art-recognized unpredictability of using the claimed

DNA constructs to reduce the levels of a predetermined protein in an animal.

In concusion, the specification is enabling for a method of neutralizing the biological function of a predetermined protein by immunizing an animal with a DNA encoding for the claimed fusion protein, and not for a method of reducing the levels of a predetermined protein by immunizing an animal with a DNA encoding for the claimed fusion protein.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> ((e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 80 and 101 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnston et al. (U.S. Patent No. 5,703,057).

Johnston et al. teach expression library immunization, wherein a cloned expression library is prepared from the fragmented DNA of a pathogen and wherein mammalian genes, such as the gene encoding for ubiquitin is fused to the DNA to facilitate expression in mammalian cells (claims 80, 94, and 101) (column 1, lines 1-14, column 3, lines 13-25, column 5, lines 19-29). The library is used to elicit immune responses in both arms of the immune system, i.e., humoral (i.e., the fusion protein is expressed) and cellular, when injected into animals (column 5, lines 30-40, column 5

bridging column 6). Since Johnston et al. teach a method for stimulating an immune response in an animal by introducing into the cells of the animal a DNA construct encoding an ubiquitin fusion protein, wherein the protein is expressed, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 80, 94-97, and 99-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al., as applied to claims 80 and 101 above, in view of Ferro et al. (Eur J Cancer, 1997, 33: 1468-1478) and Tang et al. (Nature, 1992, 356: 152-154), as evidenced by Sacca (Cardiovascular Research, 1997, 36: 3-9).

Johnston et al. teach the conjugation of the ubiquitin fusion protein with a non-ubiqiuitin carrier protein, such as KLH or BSA (claim 100) (column 24, lines 44-55). Johnson et al. do not teach neutralizing the biological function of a predetermined protein by immunizing the animals with the ubiquitin fusion protein (claim 94), wherein the predetermined protein is gonadotropin releasing hormone (claims 95-97) or a growth hormone (claim 99). Ferro et al. teach the immunoneutralization of GnRH for immunocastration and as a potential anti-tumor treatment (Abstract, p. 1475, column 1, p. 1477, column 2). Ferro et al. do not teach a DNA vaccine or a vaccine against a

growth hormone. Tang et al. teach DNA vaccines as being able to produce an efficient immune response against the human growth hormone (hGH) (Abstract, p. 152, column 2 bridging p. 153). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Johnson et al. to make a DNA vaccine, wherein the DNA encodes for a fusion ubiquitin-GnRH or ubiquitin-hGH and wherein the fusion protein is further conjugated to a non-ubiquitin carrier, with a reasonable expectation of success. The motivation to use an anti-GnRh vaccine is provided by Ferro et al. who teach the utility of immunoneutralizing GnRH for lowering the estradiol levels and therefore as a potential therapy in estrogen-sensitive disorders such as polycystic ovary syndrome and hormone-dependent breast cancer (p. 1468, column 1 bridging column 2). Additionally, one of skill in the art would have been motivated to immunoneutralize hGH because the art prior teaches that an excess of hGH is associated with certain diseases, such as acromegaly (see Sacca, p. 4, column 1 and 2). The motivation to use a DNA and not a protein vaccine is provided by Tang et al., who teach that the use of a DNA vaccine is simple and shorten the time required to produce antibodies by eliminating the steps of protein purification and adjuvant administration (Abstract, p. 154, column 1 bridging column 2). The motivation to use a DNA encoding for an ubiquitin fusion that is further conjugated with a non-ubiquitin carrier is provided by Johnston et al., who teach that ubiquitin facilitates expression in mammalian cells and a carrier enhances immunogenicity (see above). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of DNA constructs encoding for ubiquitin

fusion proteins to elicit antibody responses in animals. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

12. Claims 80, 94, 98, 100, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al., as applied to claims 80 and 101 above, in view of both Hohlfeld (Multiple Sclerosis, 1996, 1: 376-378) and Tang et al.

Johnston et al. teach the conjugation of the ubiquitin fusion protein with a non-ubiqiuitin carrier protein, such as KLH or BSA (claim 100) (column 24, lines 44-55). Johnson et al. do not teach neutralizing the biological function of a predetermined protein by immunizing the animals with the ubiquitin fusion protein (claim 94), wherein the predetermined protein is tumor necrosis factor (TNF). Hohlfeld teaches the use of antibodies to inhibit TNF-α activity as a treatment for multiple sclerosis (Abstract, p. 377, column 1 bridging column 2). Hohlfeld does not teach a DNA vaccine to raise antibodies against TNF-α. Tang et al. teach DNA vaccines as being able to produce an efficient immune responses against different proteins (Abstract, p. 152, column 2 bridging p. 153, p. 154, columns 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Johnston et al. to make a DNA vaccine, wherein the DNA encodes for a fusion ubiquitin-TNF-α and wherein the fusion protein is further conjugated to a non-ubiquitin carrier, with a reasonable expectation of success. The motivation to use an anti- TNF-α vaccine is provided by Hohlfeld who teaches the utility of immunoneutralizing TNF-α activity for the treatment of diseases such as multiple sclerosis and rheumatoid arthritis (p. 377,

column 1 bvridging column 2). The motivation to use a DNA encoding for an ubiquitin fusion that is further conjugated with a non-ubiquitin carrier is provided by Johnston et al., who teach that ubiquitin facilitates expression in mammalian cells and a carrier enhances immunogenicity (see above). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of DNA constructs encoding for ubiquitin fusion proteins to elicit antibody responses in animals. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD